

CELL CULTURE EXPERIMENTS PLANNED FOR THE SPACE BIOREACTOR*

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Many opportunities to study different cell culture technologies and downstream processing will be afforded by a multi-step bioprocessing operation in space. A typical space bioprocess would consist of: (1) a unit to separate the cells that produce a useful biochemical; (2) a bioreactor to culture these cells and isolate the culture medium containing secreted products; and (3) a unit to concentrate and purify the product. It appears that a process centered around the culture of human cells that produce hormones or other macromolecules having clinical use would be the most interesting. The first and last steps have already been demonstrated during experiments on the Space Shuttle. Human kidney cells which produce urokinase and α -PA and pituitary cells which produce growth hormone and prolactin have been separated by electrophoresis on STS-8. Commercial product purification experiments on STS-7, 41-D, 51-D, and 61-B have demonstrated the advantages of the continuous flow electrophoresis for purifying hormone products direct from concentrated culture medium. However, the intermediate step, culturing the cells in a pilot-scale bioreactor remains to be done in microgravity. An approach is presented based on several studies of cell culture systems. Next, previous and current cell culture research in microgravity is described which is specifically directed towards development of a space bioprocess. Finally, cell culture experiments now planned for microgravity sciences mission are described in abstract form.

BACKGROUND

Assessment of Different Cell Culture Systems

Conventional industrial and laboratory methods of growing human cells have been limited to systems which grow and maintain cells in a monolayer. That is largely due to the anchorage dependence of mammalian cells. Virtually all normal human cells (except for a few types) must be firmly attached to some suitable surface before they will proliferate, and eventually secrete

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products. Attempts to grow large numbers of cells on the inside surface of roller bottles and in chambers containing multiple plates have enhanced large-scale cultures, but not enough. Some additional success has been achieved by growing cells attached to spiral-wound membranes and to the inner surface of hollow-fiber dialysis bundles, in which nutrients can be supplied through the permeable membrane from media circulated on the opposite side of the membrane or hollow fiber. These techniques have difficulties with oxygenation, and difficulty in maintaining precise control of the culture environment.⁶ Also, problems of cell recovery and cleaning have made large-scale operation extremely difficult and costly. Extensive research and development programs and our own laboratory comparisons have indicated that perfusion-type suspension cultures of mammalian cells in microgravity would be highly desirable from a process control and economic viewpoint.

Some of the major problems associated with monolayer cultures are (1) growth taking place in only two dimensions (surface area), (2) cell proliferation limited by depletion of oxygen and nutrients, (3) difficulties with media circulation and volume-to-cell number ratios, (4) cell/product recovery, (5) cleaning, and (6) sterilization could be solved by using suspension culture. Unfortunately, almost all human cells of pharmaceutical interest grow quite poorly in modern suspension culture systems. Under optimum small-scale conditions, the maximum density of cells is approximately 30×10^6 cells/cm³.¹⁴ This concentration is several orders of magnitude less than the number achieved in microbial cultures. Since the amount of product formed normally is directly proportional to the number of the cells, high cell concentrations are critical to successful commercial cultures.

Currently, 150-180 micrometer diameter carrier beads are used to grow anchorage-dependent human cells in a suspension culture. The beads, with attached cells, are kept in suspension by stirring and the number of cells that can be grown is proportional to the concentration of beads that can be suspended. This can present a dilemma, however, because as the number of beads increases so does the need for mixing to provide nutrients and remove wastes. As the mixing becomes more vigorous, more cells are damaged by shear forces and bead collisions. This has led to development of new, more gentle stirring methods and reactor designs.⁴ The ultimate low shear experiments (using cells attached to microcarriers) can best be performed in microgravity, since mixing is only required to distribute nutrients and wastes. This should lead to increased viability, higher cell concentrations, longer culture runs, and perhaps more product secretions than can be achieved on Earth.

Continual supply of nutrients and oxygen is best accomplished by continuous perfusion of culture medium. Spin filter techniques⁷ have been successful for separating the cells from the spent medium in stirred suspension reactors. However, conventional spin filter systems do not suspend microcarriers well and produce high shear stress to the attached cells. Oxygen is best

supplied by circulating the medium through an oxygenator before it enters the culture vessel. A bioreactor operating in microgravity, however, is expected to offer certain advantages in the precise control of dissolved oxygen. These advantages will be discussed in the experimental abstracts below.

Experience gained from microbial fermentation also has shown that continuous cultures require precise control of environmental conditions. In mammalian cell cultures this control is even more critical. Precise maintenance of shear, nutrients, waste levels, and the microenvironment surrounding the cells also are important design criteria for a space bioreactor.

Previous Studies Undertaken by NASA

Cell culture experiments leading towards a space bioprocess have been indicated since the electrophoresis experiments on the Apollo-Soyuz Test Project (ASTP) in 1975.¹ Electrophoretic separations of intact cells would be the first step in a bioprocess (on Earth, electrophoresis of cells gives poor resolution). It was hypothesized that in microgravity the resolution would improve, because sedimentation and density-driven convection currents would be absent. A successful separation was achieved for human embryonic kidney (HEK) cells, which produce a medically-important enzyme called urokinase. One of the separated cell fractions produced six to seven times more urokinase than ever before possible under commercial tissue culture conditions.²

Urokinase activates plasminogen to produce plasmin which, in turn, dissolves blood clots after they are formed. Pharmaceutical laboratories are using large scale culture of human kidney cells to produce urokinase for clinical use. Since this agent is a protein, it is desirable for immunological reasons to use human sources. Previous laboratory studies have shown that only a small percentage of cultured kidney cells actually produce the enzyme.³ The efficiency of commercial production could possibly be enhanced if the high urokinase producing kidney cells were cultured. Kidney cells are a prime candidate for the first experiments using a space bioreactor.

During Skylab III, cultures of a strain of diploid human embryonic lung cells were studied for 28 days.¹⁰ Comparisons between cultures kept in microgravity and in 1-g showed no detectable differences in mitotic index, cell cycle, or migration. Growth curve, DNA microspectrophotometry, phase microscopy, and ultra-structural studies revealed no effects of microgravity. Although these results suggested that cells are not altered during space flight, more recent results on STS-8 indicate that cell attachment to microcarriers is significantly increased¹⁵ and that hormone secretion from mammalian cells is reduced in microgravity.⁸

In another type of experiment, the attachment of HEK cells to microcarriers was compared in microgravity and on Earth.¹⁵ This was an essential first step for devising a reactor for a suspension cell culture. The cells were still anchorage-dependent in microgravity, and although attachment was increased, proliferation on the beads occurred normally during the first 24 hours.

The basic concepts for a space bioreactor were proposed in 1977 based on extensive experience with terrestrial fermentation systems.¹² One important idea was that oxygen transport would be faster than in microgravity. This was based on the work by Fester et al., who found that surface tension forces insignificant in 1-g become important in microgravity.⁵ A second idea was a sophisticated process control scheme, which would maintain the rigorous environmental control required by mammalian cells, but minimize operator (astronaut) attention. In 1978-79, under contract to NASA, Arthur D. Little, Inc., conducted two workshops to define the scientific principles involved in the production of biologicals from cells in microgravity and to identify specific advantages or disadvantages of attempting cell culture biosynthesis of a specific biological product under microgravity conditions. The workshop participants identified factors that constrained large scale mammalian cultures and selected those that should be relieved by microgravity. They then proposed experiments to explore these factors. The most important categories were

- Shear effects (mixing, flow patterns, gas transfer, etc.)
- Microenvironment
- Techniques to increase cell density

Categories of secondary interest were

- Use of primary cells or cell lines
- Genetic selection in microgravity
- Anchorage dependence in microgravity

Finally, interested participants were asked to propose systems that could be used to develop specific experiments. Pituitary cells were one proposal, which led to the electrophoresis separation experiments conducted on STS-8.

Although cell culture process technology has evolved rapidly, the factors that constrain large-scale culture still apply. At a "Workshop of Bioprocess Scale Up" held in late 1983, participants discussed several of the problems that the space bioreactor is being designed to explore.¹⁴

Studies Now in Progress

The conceptual studies made it clear that the development of a space bioreactor would require a collaborative effort with university and industrial partners. Recognition of this led to the development of a Space Bioreactor Laboratory at JSC. Over the last 8 years, JSC has used in-house research, cooperative research with industry and academia, and symposia to build a body of information pertinent to conducting cell culture and cell biology research in space. The conceptual design for the bioreactor is being reduced to practice now under a plan to flight test the system in Spring 1988. (See figure 12-1.)

The basic design is a perfusion reactor with a new version of a spin filter (Virtis Co.), combined with a stirring vane similar to that described by Feder and Tolbert.⁴ The reactor is designed to operate with no headspace. Sensors for pH, dissolved oxygen, CO₂, and pressure are located outside the reactor vessel before and after the reactor in a medium circulation loop. This provides for differential measurements across the reactor and simplifies control of turbulence and shear within the reactor. Figure 12-2 shows an early version of the bioreactor test unit.

In the cell-free medium circulation loop are vessels for oxygenation, separation of wastes, and isolation of a high molecular weight product. Concentration of the crude product will be required before final purification by CFES. The process control scheme is being modelled. Primary HEK cells attached to microcarrier beads will be used for early runs. They will be maintained on serum-free medium rather than in a growth mode. Reliable assays for plasminogen activators have been developed for kidney cell separation experiments in microgravity.¹¹ Several design criteria are imposed by the design of the Shuttle Orbiter. Compactness, energy efficiency, and a self-sufficient process controller are required. The assembled bioreactor (less the process controller) must be autoclaved shortly before loading cells and installing the bioreactor in the middeck of the Orbiter. This has limited the choices of pump, sensor probes, and other parts.

Various academic research studies have been initiated by the Principal Investigator (D. R. Morrison) to consider the effect of microgravity on the process. (See table 12-1.) The collaboration of Baylor College of Medicine, Rice University, and the University of Houston has been arranged through the new Bioprocessing Research Center at the University of Texas Health Science Center at Houston (UTHSC). This grant also provides for operation of a ground-based CFES unit, for study of alternative separation techniques, studying shear and mixing in the reactor vessel, and developing aspects of the process control system. Some preliminary results on the effect of shear stress on HEK cells have been reported.¹³ The maximum shear force tolerated by the cells was determined as well as the shear range which caused changes

in cell morphology. More interestingly, it was concluded that increasing the shear stress and then lowering it again stimulated release of urokinase.

OBJECTIVES

The following experimental objectives are now envisioned for early flights of a space bioreactor.

Conduct cell culture experiments to:

- Study shear regimes that are too low to achieve in 1-g
- Measure the effects of shear forces on a cell membrane and function
- Explore novel culture systems using controlled gas/liquid or liquid/liquid suspensions
- Study transfer of gases to and from the cells in mass culture
- Gain insight into the physical interactions occurring in microgravity among gaseous O_2 , liquid media, and CO_2 from cell metabolism

Finally, a space bioreactor can be used to grow and to maintain cells to support development of new cell separation methods and cell biology research in the microgravity environment.

ABSTRACTS

The following abstracts are examples of cell culture studies being developed for flight experiment proposals to be conducted on the Space Shuttle before 1990. Two ground support research projects are also included.

EFFECTS OF PRESSURE AND SHEAR STRESS ON CULTURED CELLS (D. R. Morrison, JSC, R. M. Nerem, Univ. Houston, L. V. McIntire, Rice Univ.)

- Hypothesis

Mechanical stress exerted on cells at less than the force required to rupture the cell membrane will result in changes in cell morphology and membrane mechanical properties. It may cause increased release of product proteins or stress response proteins.

- Rationale/justification

Data from endothelial cell cultures show that prostaglandin secretions can be stimulated to 16 times normal by proper shear stress regimes. Stathopoulos and Hellums reported a relationship between shear force and urokinase release by HEK cells.¹³

- Objectives

- To develop techniques wherein appropriate regulation of shear forces stimulates the release of target products from the cells
- To understand mechanisms of damage to suspension cultures of mammalian cells and to devise improved methods for culture in a stirred suspension reactor

- Proposed experiments

Using the flow chamber described by Stathopoulos and Hellums,¹³ we will run the following studies:

- Flow chamber study of the effects of various fluid shear stresses on cultured monolayer kidney cells
- Studies of changes in morphology and cellular alteration before, during, and after each short or long exposure to a laminar flow field

Under the contract with the Bioprocessing Research Center at UTHSCH, Robert M. Nerem and Murina J. Revesque, University of Houston, have proposed several experiments:

- Determine the effects of pressure and shear stress on cultured kidney cells, including the influence of the degree of confluency, age, passage number, etc.
- Evaluate the effects of different substrates on the tolerance of cultured kidney cells to shear stress and the influence of shear
- Measure the mechanical properties of cultured kidney cells and the change in such properties due to the influence of shear
- Conduct experiments whose purpose will be to determine the behavior of cultured kidney cells on suspended microcarrier beads in the presence of a known shear stress imposed by flow through a parallel plate, channel flow device.

THE EFFECT OF UNIQUE FLUID DYNAMIC PROPERTIES ON CELLS CULTURED IN MICROGRAVITY (D. R. Morrison, JSC)

- Hypothesis

Microgravity will alter the effective mass transfer coefficients for transfer of O_2 (g) into medium and from medium to a cell or enzyme in a slowly stirred suspension culture system.

- Rationale/justification

Fester et al. proposed that certain surface tension forces insignificant in 1-g will alter fluid behavior in space.⁵ Mattoni observed enhanced growth of microorganisms in microgravity.⁹ Nyiri attributed this to better O_2 transfer in the microgravity environment.¹²

- Objective

Measure mixing characteristics and phase-transfer phenomena in a bioreactor equipped with special instrumentation.

- Proposed experiment

Compare the rate of the enzymatic oxidation of glucose to D-glucose- γ -lactone in space and on Earth, proposed by Nyiri¹² (proposal in response to NASA AO-77-3) based on a technique of Weibel and Bright.¹⁶ Preliminary work has already been done by Charles and Nyiri (midterm report of contract NAS 9-15619, 1979).

- Issues

This study may be a necessary part of fine tuning the mixing and oxygenation components of the bioreactor before a cell culture can be adequately sustained under fully optimum conditions in microgravity.

CULTURE OF CELLS IN A CONTROLLED FOAM IN THE ABSENCE OF BUOYANCY (D. R. Morrison, JSC)

- Hypothesis

A steady-state condition can be achieved in a space bioreactor such that a foam can be maintained by introduction of oxygen bubbles and generation of CO_2 . The very high stability of this foam will allow a unique opportunity to culture cells in the liquid phase directly adjacent to air or oxygen bubbles without the usual disadvantage of bubble buoyancy.

- Rationale/justification

In experiments done in Apollo spacecraft, foams were easier to generate and were more stable than on Earth. This hypothesis carries these observations to a novel, practical application.

- Objectives

- To characterize O_2 transport from gas bubbles to cells in the absence of buoyancy
- To find better ways to transport O_2 to living cells in a stirred suspension reactor

- Issues

Oxygenation of cell culture in 1-g is very inefficient because the densities of O_2 (g) and H_2O (l) differ greatly, and because the bubbles of oxygen coalesce readily. Since oxygen has very low solubility in aqueous medium, sparging rates must be high to deliver enough oxygen. High sparging rates, in turn, cause high shear which leads to cell damage.

CULTURE OF CELLS USING FLUOROCARBON OXYGENATORS IN ABSENCE OF DENSITY-DRIVEN SEPARATION (D. R. Morrison, JSC and W. B. Armiger, Bio-Chem Technologies, Inc.)

- Hypothesis

Oxygen and CO_2 are quite soluble in certain fluorocarbon liquids which are very dense (S.G. = 1.7).

It is proposed that oxygen distribution to cell cultures can be enhanced by dissolving it in immiscible fluorocarbons which can be dispersed in the aqueous medium. Since the dispersion will be stable in microgravity, it will be possible to study this novel oxygenation technique properly.

- Rationale/justification

This concept has been tried with terrestrial cultures by Bio-Chem Technologies (Malvern, Pennsylvania). Although density differences caused rapid separation of the two phases, the fluorocarbons dissolve a relatively large amount of O_2 and do provide more O_2 to microbial cells in a suspension type fermentor.

- Objective

To explore better ways to oxygenate cell cultures. To simplify development of practical methods, data from experiments in microgravity may aid implementation of this system in terrestrial cultures. Additional data will, of course, be gained on liquid/liquid interactions as opposed to the liquid/gas interactions in the preceding abstract.

- Issues

- This seems to be an ideal candidate for evaluation in a space bioreactor.
- Need to develop method of dispersion and characterize how long emulsion will remain intact in microgravity.

PHYSIOLOGY OF CELLS CULTURED IN MICROGRAVITY (D. R. Morrison, JSC and R. M. Nerem, Univ. Houston)

- Hypothesis

Cells cultured in the absence of gravity may adapt in ways that are expressed in changes in cell morphology or biochemical functions.

- Rationale/justification

Early experiments with cells growing under weightlessness indicated that the cell density of Salmonella typhimurium was significantly higher than on Earth.⁹ The increase was attributed to enhanced efficiency of nutrient transfer to and waste product removal from the cells. Also cell attachment to microcarriers was significantly increased shortly after being mixed together in microgravity.¹⁵ On the other hand, the study of diploid human embryonic lung cells showed no changes from an Earth control.¹⁰ A long-term study is required to find and characterize any changes in cell structure and function.

- Objective

Measure a variety of morphological and biochemical characteristics of cells on Earth and after acclimation to microgravity. Planned analyses include 2-D electrophoretic mapping of intracellular proteins, cell survival, cell attachment to beads, secretion of natural cell products, total protein concentration, DNA and RNA content, and examination of the cytoskeleton.

- Issue

This may have a bearing on long-term effects of microgravity on humans.

GROUND SUPPORT RESEARCH PROJECTS

ANALYSIS OF THE PROTEINS PRODUCED BY HEK CELLS (D. R. Morrison, JSC and M. Z. Atassi, Baylor College of Medicine)

- Hypothesis

Analytical methods can be devised to separate and quantify a mixture of proteins, which includes several forms of the plasminogen activators and their inhibitors.

- Rationale/justification

Bioassays exist, but these do not measure proenzyme (inactive) nor inhibitors. Specific methods exist for plasminogen activators, but other proteins could escape detection. A means of rapidly assessing the protein production of the bioprocess is desirable.

- Objective

- Develop rapid, general analyses for the high molecular weight fraction that will be the product of the bioreactor. Detect changes in the composition of this fraction.
- Use the bioreactor to provide secreted protein products for purification in space using the McDonnell Douglas CFES apparatus or other NASA sponsored techniques for bioseparation in microgravity.

- Issues

- The proteins involved are roughly similar. Their separation will be a challenge probably requiring CFES, high pressure liquid chromatography (HPLC), or other special techniques.
- A chromatographic method is desirable as an interim step because it allows quantitative analysis of new compounds or loss of old ones as the process changes.
- A radioimmunoassay for urokinase and related compounds is being developed by Dr. Zouhair Atassi, Baylor College of Medicine, under the UTHSC contract NAS9-17403.

- The UTHSC has a task to perfect CFES separation of urokinase from culture medium.
- Methods are needed for the development phase as well as the operational phase.

PROCESS CONTROL SCHEMES FOR A MAMMALIAN CELL CULTURE (C. F. Goochee, Univ. Houston, K. Y. San, Rice University, and D. R. Morrison, JSC)

- Hypothesis

That the requirements for maintenance of these cells are rigid enough to warrant an advanced type of process control.

- Rationale/justification

Existing schemes are not capable of the degree of feedback needed to control a bioreactor through growth and production phases.

- Objective

Automatic control of the bioreactor from inoculation through growth phase into production phase.

- Experiments proposed

Modelling of the process control scheme is being conducted by Dr. Goochee, University of Houston, under the UTHSC contract. The control scheme proposed by the principal investigator has a loop that controls variables such as pH, dissolved oxygen, CO₂, redox potential, and a supervisory loop that detects and connects changes in the metabolic activity of the cell. A fluorescent device to measure cell metabolism by NADH₂ concentration (Bio-Chem Technology, Malvern, Pennsylvania) will be the first element of this loop to be tested by Dr. Morrison at JSC. Dr. Ka-Yiu San, Rice University, also is investigating design aspects of the controller scheme under the UTHSC contract.

- Issues

The monitored parameters and control strategy for a space bioreactor probably applies to ground-based systems as well.

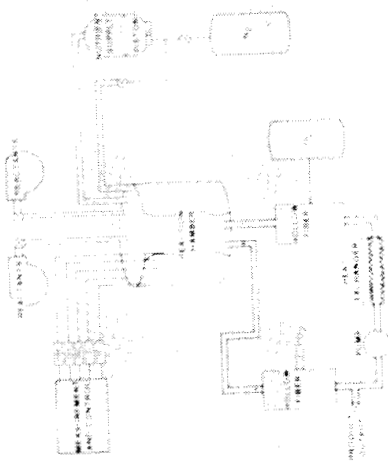
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TABLE 12-1.- UNIVERSITY SUPPORT TASKS FOR BIOREACTOR

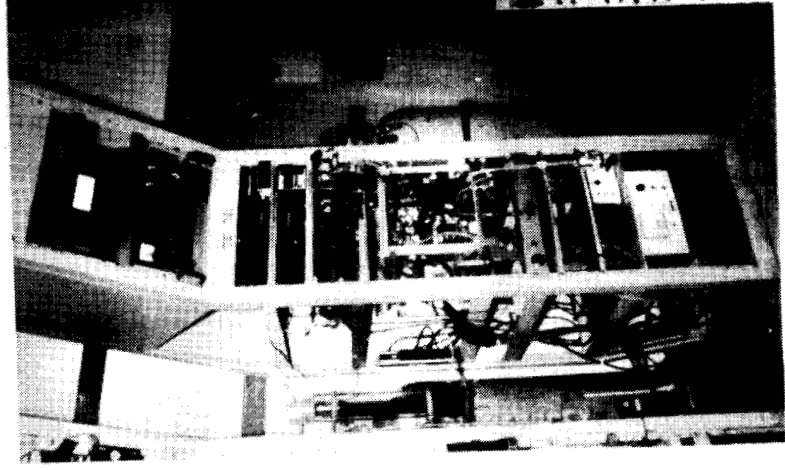
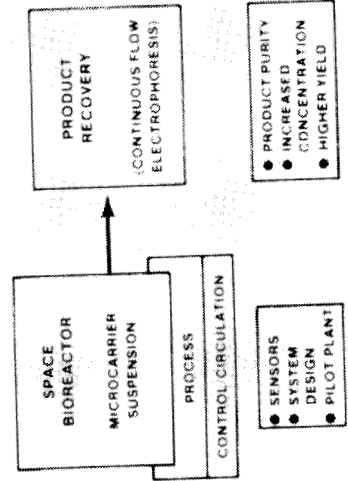
<u>TASK</u>	<u>CONTRACTOR</u>
1. ANALYSIS OF CELL CULTURE MEDIUM	BAYLOR COLLEGE OF MEDICINE CELL AND PROTEIN CHEMISTRY LAB (DR. M. Z. ATASSI)
2. SCREENING OF NEW CELL LOTS	PENN STATE UNIVERSITY BIOPHYSICS LAB (DR. P. TODD)
3. FLUID AND GAS DYNAMIC ANALYSIS	U. OF HOUSTON CHEM. ENG. DEPT. (DR. C. GOOCHEE)
4. EFFECTS OF SHEAR ON CELLS AND UK PRODUCTION	RICE UNIV./BAYLOR/IN-HOUSE (DR. KALMAZ - NRC). AND PROCESS CONTROL SYSTEM READY
5. FLUOROMEASURE OF CELL METABOLISM	UNIV. CITY SCI. CENTER (PHIL.) BIOCHEM. TECHNOLOGIES, INC. (DR. BILL ARMIGER)
6. FLUID DYNAMIC STUDIES	U. OF HOUSTON MECH. ENG. DEPT. (DR. R. NEREM)
7. SENSORS, MIXING AND CONTROL SYSTEMS	RICE UNIVERSITY DEPT. CHEM. ENG. (DRS. L. McINTIRE AND T. PAPOUTSAKIS)



CONCEPTUAL DESIGN OF ZERO-G BIOREACTOR - USES:

- DEMONSTRATE TECHNOLOGY IMPROVEMENTS BY ELIMINATING SEDIMENTATION OR BUBBLE BOUYANCY
- CULTURE OF HUMAN CELLS TO OBTAIN HORMONES OR OTHER MEDICAL PRODUCTS
- TANDEM OPERATIONS WITH CONTINUOUS FLOW ELECTROPHORESIS (CFES)
- GROWTH/MAINTENANCE OF CELLS FOR SPACE BIOLOGY EXPERIMENTS

IN ZERO-G



- BIOREACTOR VERIFICATION TEST UNIT**
- PROPOSED FOR MIDDECK VERIFICATION TEST IN 1985**
- MICROGRAVITY OPERATIONS
 - BIOMASS CHAMBER
 - FLUID CIRCULATION SYSTEM
 - SENSOR CONTROL SYSTEM

SPACE BIOREACTOR

- SINGLE SPACELAB RACK OR MIDDECK - 3 LOCKER SYSTEM
- SELF CONTAINED DATA RECORDING
- MICROPROCESSOR CONTROLLED OPERATIONS

GROUND BASED PROTOTYPE BIOREACTOR

- SENSOR DEVELOPMENT
- MICROPROCESSOR CONTROL PARAMETERS

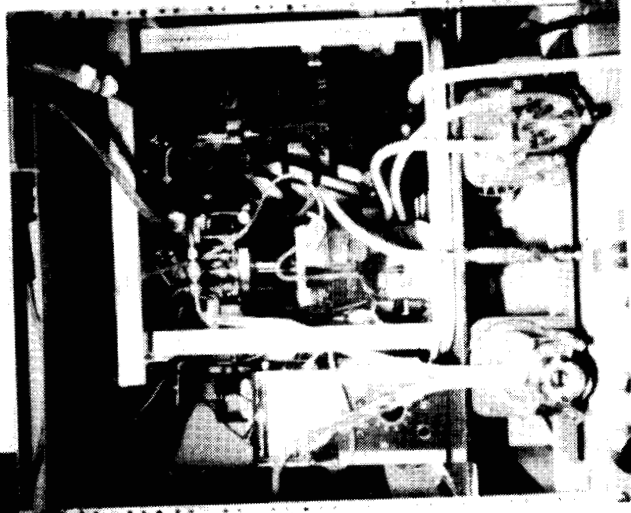


Figure 12-1.- Space bioreactor for cell cultures.

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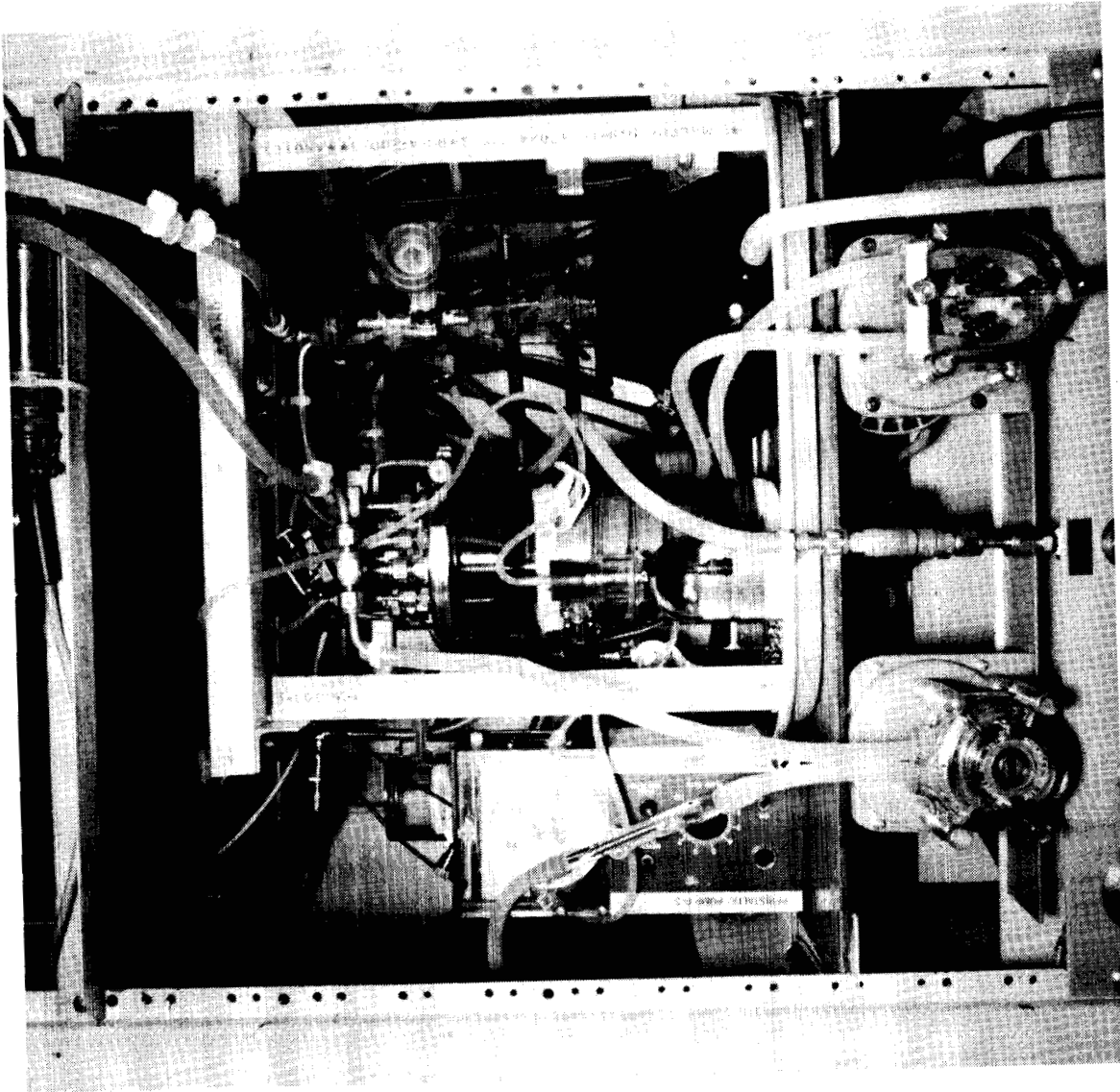


Figure 12-2.- Bioreactor verification test unit.